NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

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RFA: RFA-AR-01-007

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: November 2, 2001
Application Receipt Date: December 14, 2001

THIS RFA USES "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. USE THE MODULAR BUDGET INSTRUCTIONS THAT BEGIN ON PAGE 13 IN THE PHS 398 (REVISION 5/2001) AVAILABLE AT http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invites applications for research on the pathogenesis of neuropsychiatric manifestations of systemic lupus erythematosus (NP-SLE) and on the development of innovative therapeutic approaches and diagnostics for this form of lupus. The applications may be for individual research projects (R01) or for exploratory/developmental grants (R21). Systemic lupus erythematosus (SLE) is a multi-system rheumatic disease with a wide variety of associated clinical neurological and psychiatric syndromes including cognitive, behavioral, affective, and/or motor manifestations that may affect up to 75 percent of SLE patients. Both morbidity and mortality remain high because of lack of understanding of the underlying mechanisms related to abnormal central nervous system (CNS) function. In addition, progress has been hampered by the lack of specific diagnostic methods and therapeutic regimens. This RFA is based in part on the scientific opportunities identified in the conference "CNS Manifestations of Systemic Lupus Erythematosus." A summary of the conference and research questions raised can be found at http://www.nih.gov/niams/reports/reportnmsle.htm.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain

"Healthy People 2010" at http://www.health.gov/healthypeople. The two overarching goals of Healthy People 2010 are to (1) increase quality and years of healthy life and (2) eliminate health disparities.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and nonprofit organizations, public or private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal Government. Applicants also may collaborate, through consultation or contractual agreements, with investigators at foreign institutions. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

The mechanisms of support will include the investigator-initiated research project grant (R01) and the exploratory/developmental research grant (R21).

R21 Applications. The purpose of the R21 projects solicited under this RFA is to gather preliminary data leading to the development of an investigator-initiated research project (R01). Use of this mechanism is recommended by investigators experienced in lupus research who wish to adapt or apply neuroscience, vascular biology or other relevant methodologies to study NP-SLE pathogenesis. It is also recommended for investigators with relevant expertise (e.g., neuroscience, behavioral, vascular biology or others) interested in developing a program in NP-SLE. In addition, the R21 mechanism can be used for projects where the aim is to gather pre-clinical data for new therapies.

Exploratory/developmental studies are not intended for large-scale undertakings or to support or supplement ongoing research. Instead, investigators are encouraged to explore the feasibility of an innovative research question or approach that may not be at a stage advanced enough to compete as a standard research project grant (e.g., R01). The R21 mechanism can also be used to develop a research basis for a subsequent application through other mechanisms, i.e., R01, P01.

Exploratory/developmental (R21) grants may not exceed $75,000 per year in direct costs, not including facilities and administrative (F&A) costs for collaborating institutions, if any. The total project period for an R21 application submitted in response to this RFA may not exceed 3 years.

These grants are nonrenewable and continuation of projects developed under the R21 program will be through the traditional unsolicited (R01 or P01) grant programs.

Investigators proposing to conduct small, pilot/toxicity clinical trials are advised to review the NIAMS guidelines for preparation of clinical trial applications and the NIAMS guidelines for data and safety monitoring boards (http://www.nih.gov/niams/clinical/dsmb3.html).

R01 Applications. The individual research grant (R01) is a specific, circumscribed project to be performed by the named investigator(s) who has a specific interest and competency in an area of interest to this RFA. The total project period for an R01 application submitted in response to this RFA may not exceed 5 years. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to the customary peer review procedures.

Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an R01 award will vary also. Modular budgeting procedures apply for grants up to $250,000. Specific R01 application instructions have been modified to reflect "modular grant" and "just-in-time" streamlining efforts. Complete instructions and information on modular grants can be found at http://grants.nih.gov/grants/funding/modular/modular.htm. Direct costs will be awarded in modules of $25,000, less any overlap or other necessary administrative adjustments. F&A costs will be awarded based on the negotiated rates.

Investigators who wish to establish new collaborative research programs in NP-SLE with laboratories at the NIAMS Intramural Research Program, and apply for funding under this RFA, are encouraged to contact Dr. Barbara Mittleman, Director, Office of Scientific Interchange, NIAMS (mittlemb@mail.nih.gov).

FUNDS AVAILABLE

It is anticipated that for FY 2002, approximately $1.2 million total costs will be available for the first year of support for this initiative. The specific number to be funded will depend on the merit and scope of the applications received and on the availability of funds. Applicants may request up to 5 years of support for the R01. Exploratory/developmental (R21) grants may not exceed $75,000 per year in direct costs, not including F&A costs for collaborating institutions, if any. The total project period for an R21 application submitted in response to this RFA may not exceed 3 years. These grants are non-renewable and continuation of projects developed under the R21 program will be through the traditional unsolicited (R01 or P01) grant programs.

RESEARCH OBJECTIVES

NP-SLE is an ill-understood clinical manifestation of systemic lupus erythematosus and constitutes one of the major causes of death among lupus patients. Clincal expression of NP-SLE is diverse, may be intermittent or progressive, and can range from mild to severe. NP-SLE manifestations include diffuse encephalopathy, depression, cognitive dysfunction, memory loss, concentration deficits, dementia, anxiety syndromes, cranial neuropathies, cerebrovascular accidents, transverse myelitis, seizures, headaches, aseptic meningitis, pseudotumor cerebri, and lupoid sclerosis. In general, a fluctuating course of disease rather than a rapid decline to dementia is characteristic. Cognitive impairment can occur in isolation or in the context of other neurologic or psychiatric syndromes such as depression or psychosis. The American College of Rheumatology (ACR) has developed a standard nomenclature for NP-SLE [Arth. Rheum., 1999, 42(4):599-608] using a 1-hour battery of neuropsychological tests of cognitive function.

Certain deficits are specifically associated with particular serum autoantibodies. In recent reports, lupus psychosis was found to be associated with the presence of antibodies directed against the carboxyl terminus of the ribosomal P proteins. A shared amino acid sequence between HLA-DQB1 and P peptides was strongly associated with anti-P antibodies in SLE, suggesting the presence of autoreactive T cells directed against P proteins. The mechanisms explaining these associations and their contribution to disease pathogenesis are uncertain. Antibodies may bind to cell-surface receptors on neuronal cells, and autoreactive T cells may produce cytokines that may contribute to organ inflammation. Vascular events also appear to contribute to CNS involvement in lupus. Intravascular thrombosis and vasculitis have been found associated with NP-SLE. Other not-yet-defined mechanisms may also be involved.

With the recent development of diagnostic and classification criteria for NP-SLE, clinical research can now proceed to establish other associations with immune and nonimmune mechanisms of disease. Research in this area could improve significantly with the development of new techniques to assess organ involvement and with the development of new animal models to explore the pathogenesis of the disease.

The purpose of this announcement is to encourage exploratory/developmental projects (R21) and investigator initiated research projects (R01) that explore new approaches and hypotheses on the pathogenesis of NP-SLE. Further, projects exploring the natural history of the disease, new diagnostic modalities, and therapeutics are also encouraged. Areas of interest include but are not limited to:

o Studies designed to discover the underlying mechanisms of nervous system involvement in SLE, including studies in new and existing animal models of disease.

o Advanced research projects to further describe clinical features of NP-SLE and establish correlations with systemic and other organ manifestations, for example, correlation between CNS and peripheral vasculopathies.

o Hypothesis-generating studies of murine and human NP-SLE to examine the role of inflammatory mediators and inflammation of the central nervous system and/or its vasculature in NP-SLE pathophysiology, e.g., endothelial activation, immune complex deposition and effacement of the blood-brain barrier, extracellular matrix components, pericyte and microglial activation, abnormalities in neurotransmission and neurophysiology, autoantibodies such as antiphospholipid antibodies, abnormalities of coagulation, etc.

o Studies aimed at dissecting the relative role of the immune and vascular processes in pathogenesis of NP-SLE.

o Epidemiology studies of NP-SLE, including studies of natural history of disease and disease outcomes, and influence of ethnicity and race in disease incidence and outcomes.

o Studies to characterize the cognitive, behavioral, affective, and motor manifestations of NP-SLE and their relations to disease outcome and quality of life.

o Assessment of structural and functional aspects of the nervous system in SLE (i.e., by neuroimaging or neuropathology).

o Evaluation of prospective biomarkers of CNS involvement in lupus, including biological, imaging, and other modalities that reflect normal or abnormal biological processes potentially relevant to NP-SLE, with emphasis on those that distinguish transient or reversible vs. irreversible processes.

o Treatment studies and linked pathophysiology research projects for prevention of damage and progressive deficits.

o Neurobehavioral evaluation of murine models of SLE.

o Evaluation of neurobehavioral effects secondary to SLE treatment.

o Development and pilot testing of new therapeutic approaches, including alternative and complementary medicine.

NOTE: Research project proposals in NP-SLE may include resource development, e.g., organizing core reference laboratories and/or reagents for specific tests, shared data collection protocols, possible central data analysis, and databases. However, the development of the core should not be the sole focus of the application.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html); a complete copy of the updated guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm. The revisions relate to NIH defined Phase III clinical trials and require (a) all applications or proposals and/or protocols to provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and (b) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Investigators also may obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998. All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the Inclusion of Children as Participants in Research Involving Human Subjects that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html.

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. This policy announcement is found in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000, at the following website: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at: http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

LETTER OF INTENT

Prospective applicants are asked to submit, by November 2, 2001, a letter of intent that includes a descriptive title of the proposed research; the name, address, and telephone number of the principal investigator; the identities of other key personnel and participating institutions; and the number and title of this RFA. Although a letter of intent is not required, the information that it contains allows Institute staff to estimate the potential review workload. The letter of intent is not binding, does not commit the sender to submit an application, and does not enter into the review of a subsequent application. The letter of intent is to be sent (e-mail, fax, or post) to Dr. Tommy Broadwater at the address listed under INQUIRIES.

APPLICATION PROCEDURES

The PHS 398 research grant application instructions and forms (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.pdf is to be used in applying for these grants. This version of PHS 398 is available in an interactive, searchable PDF format. Although applicants are strongly encouraged to begin using the 5/2001 revision of the PHS 398 as soon as possible, the NIH will continue to accept applications prepared using the 4/1998 revision until January 9, 2002. Beginning January 10, 2002, however, the NIH will return applications that are not submitted on the 5/2001 version. For further assistance contact GrantsInfo, Telephone 301/435-0714, Email: GrantsInfo@nih.gov.

STEP-BY-STEP INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and NIH staff. The research grant application form PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.pdf is to be

used in applying for these grants, with the modifications noted below. Applicants are permitted, however, to use the 4/1998 revision of the PHS 398 for scheduled application receipt dates until January 9, 2002. If you are preparing an application using the 4/1998 version, please refer to the step-by-step instructions for Modular Grants available at http://grants.nih.gov/grants/funding/modular/modular.htm.

The RFA label available in the PHS 398 (rev. 5/2001) application form (http://grants.nih.gov/grants/funding/phs398/labels.pdf) must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked.

Applications must be received by December 14, 2001. Applications not received as a single package on the receipt date or not conforming to the instructions contained in PHS 398 (rev. 5/01) Application Kit (as modified in, and superseded by, the special instructions below, for the purposes of this RFA) will be judged nonresponsive and will be returned to the applicant.

If the application submitted in response to this RFA is substantially similar to a grant application already submitted to the NIH for review that has not yet been reviewed, the applicant will be asked to withdraw either the pending application or the new one. Simultaneous submission of identical applications will not be allowed, nor will essentially identical applications be reviewed by different review committees. Therefore, an application that is essentially identical to one that has already been reviewed cannot be submitted in response to this RFA. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

Submit a signed, typewritten original of the application, including the checklist, and three signed, exact, single-sided photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040 - MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express mail or courier service)

At the time of submission, two additional exact copies of the grant application and all five sets of any appendix material must be sent to Dr. Tommy Broadwater at the address listed under INQUIRIES.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC program director or principal investigator should be included with the application.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the NIH Center for Scientific Review and for responsiveness by NIAMS staff; those judged to be incomplete or not in the format specified in this RFA will be returned to the applicant without review. Those considered to be nonresponsive will be returned without review.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NIAMS in accordance with the review criteria stated below. As part of the initial merit review, a process will be used by the initial review group in which all applications will receive a written critique but only those applications deemed to have the highest scientific merit will be discussed, assigned a priority score, and receive a second-level review by the National Advisory Council of the NIAMS.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. The reviewers will comment on the following aspects of the application in their written critiques in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered by the reviewers in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have a major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

2. Approach. Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

4. Investigator. Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

1. The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

2. The reasonableness of the proposed budget and duration in relation to the proposed research.

3. The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o scientific merit (as determined by peer review)
o availability of funds
o programmatic priorities

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome. Direct inquiries regarding programmatic issues to:

Elizabeth Gretz, Ph.D.
Director, Immunology and Inflammation Program
Rheumatic Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A19J
Bethesda MD 20892-6500
Telephone: (301) 594-5032
Fax: (301) 480-4543
Email: gretze@mail.nih.gov

Deborah Ader, Ph.D.
Director, Behavior and Prevention Research Program
Rheumatic Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A19H
Bethesda MD 20892-6500
Telephone: (301) 594-5032
Fax: (301) 480-4543
Email: aderd@mail.nih.gov

Direct review inquiries to:

Tommy Broadwater, Ph.D
Chief, Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A25U
Bethesda, MD 20892-6500
Telephone: (301) 594-4953

Fax (301) 480-4543
Email: broadwat@mail.nih.gov

Direct inquiries regarding fiscal matters to:

Melinda Nelson
Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A49F
Bethesda, MD 20892-6500
Telephone: (301) 594-3535
Fax (301) 480-5450
Email: nelsonm@mail.nih.gov

Schedule:

Letter of Intent Receipt Date: November 2, 2001
Application Receipt Date: December 14, 2001
Peer Review Date: March 2002
Council Review: June 21, 2002
Earliest Anticipated Start Date: July 1, 2002

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The Public Health Service strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or, in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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